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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,561	11/11/2003	David A. Williams	7037-485	5476

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EXAMINER

HIRIYANNA, KELAGINAMANE T

ART UNIT	PAPER NUMBER
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1633

DATE MAILED: 05/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/705,561

Applicant(s)

WILLIAMS, DAVID A.

Examiner

Kelaginamane T. Hiriyanne

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 November 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 3-9 and 16-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 3-9 and 16-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>12/2/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Specification

Priority date for this invention, applied under 35 USC §119 (e) for the provisional Application serial number 60/024,169 filed on 08/19/1996.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 16 recites its dependence to method claim 3. However, claim 3 is a product claim for "A viable cellular population". Thus claim 16 and its dependent claim 17 are indefinite.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 5, 8-9 and 18-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of cellular engrafting a non-human mammal with a viable cells that are transduced with a retrovirus, does not provide enablement for any methods for the treatment or therapy of any disease. It does not enable any person skilled in the art to which it pertains, or with which it is most

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nearly connected, to practice the invention commensurate with the full scope of the claims as explained below.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the prior art; (4) The level of one of ordinary skill; (5) The level of predictability in the art; (6) The amount of direction provided by the inventor; (7) The existence of working examples; and (8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. In *re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). All of the *Wands* factors have been considered with regard to the instant claims, with the most relevant factors discussed below as to show that one of ordinary skill in the art has to go through "undue experimentation" in order to practice the invention.

Nature of the invention: The invention relates to genetically engineering the somatic stem cells with retroviral vectors and engrafting or ex vivo therapy with said engineered cells.

Breadth of the claims And Guidance of the Specification and The scope and breadth of the instant claims, read in the light of instant specification and the state of the art at the time of filing encompass all mammalian organisms and all their cell types, a method genetic engineering using any and/or all retroviruses or retroviral based vectors in presence of any ligand that binds said cells and any/ and or all ligands that binds said retrovirus and increase transduction efficiency and further encompass engrafting or transplanting said cells to any mammalian subject in any region of the said mammalian body and by any routes of administration.

The specification provides by means of specific examples guidance and/or evidences regarding transduction of hematopoietic progenitors or stem cells of bone marrow origin (example 2 and 3) or cord blood cells (example 4) with a retroviral vector that is of non-lentiviral origin and in the presence of fibronectin fragments (example 1). Specification further provides guidance to engraftment of the retroviral transduced cells

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into mouse by injection of cells into tail veins (example 7) and long-term bone marrow reconstitution in mice (example 11). Example 8-10 and 12 deal with the mechanism of retroviral transduction enhancement by fibronectin (FN 30/35). The only disclosed utility in context of the invention as claimed is ex-vivo gene therapy.

The specification does not present enabled evidences for broad claims on methods of engraftment of any type of cells (i.e. xenotransplantations etc) to other than non-human mammals.

The specification thus fails to provide an enabling disclosure for the full scope and breadth of the invention as claimed. In the absence of adequate description of the enabled invention commensurate with the breadth and scope of the claim one of ordinary skill in the art would conclude that the claimed invention is unpredictable and would require an undue amount of experimentation to practice the full scope of the same. Applicants' attention is drawn to *In re Shokal*, 242 F.2d 771, 113 USPQ 283 (CCPA 1957). The test is whether the species completed by applicants prior to the reference date or the date of the activity provided an adequate basis for inferring that the invention has generic applicability.

The level of one of ordinary skill in the Art at the Time of Invention: The level of one of ordinary skill in the art at the time of filing of the instant application is high requiring an advanced degree or training in the relevant field. The status of the art at the time of filing was such that said skilled in the art would not have been able to make or use the invention for its fully claimed scope without undue experimentation.

State of the Art, the Predictability of the Art: At about the effective filing date of the present application art is unpredictable with regard to gene therapy and methods of in vivo gene transfers using vectors of both viral and non-viral nature. Art is still unpredictable with regard to efficacy, specificity and safety. Gene therapy or in vivo gene transfers are still considered to be highly experimental area of research and it has been difficult to predict the out come of many therapeutic genes and vector systems because of various factors that govern the expression, therapeutic potential of the transduced genes, and the undesirable host immune reactions etc., in vivo (Reviewed in Goncalves et al, Bioessays, 2005, 27: 506-517). In addition there exists an

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unpredictability about the degree to which a foreign gene or vector would interfere with cellular genetic material as observed in treatment of X-SCID patients “ These serious adverse events presented as a leukemia-like syndrome were surprising since the risk of insertional oncogenesis was considered to be negligible based on previous trials and on the perceived, though not universally accepted, notion of random retroviral integration” (Goncalves, Bioessays, 2005, 27: 506-517, p. 514, col.2, 1st ¶). Thus the unpredictability in the art, at the time of instant filing, regarding the methods and consequences of claimed ex vivo and in vivo gene therapies with retroviral vector is such that one of ordinary skill in the art finds the claimed invention highly unpredictable and cause undue experimentation to practice the invention in its full claimed scope.

Amount of experimentation necessary: These claims are not enabled because one of skilled in the art would not be able to rely upon the state of the art in order to successfully predict a priori the in vivo all the effects of the retroviral vectors or the retroviral-transduction of transgene or its fragments in a subject. One of ordinary skill in the art would be required to perform a large amount of experimentation to make and/or use the invention safely in its full scope as claimed by the Applicant (i.e. xenotransplantation etc). Such experimentation would be required to identify gene therapy effects of providing various claimed fragments of retroviral transgenes or the stem or progenitor cells transduce with said vectors or gene and determine whether such cells would provide effective and safe treatment of undisclosed conditions encompassing all cell types especially in human mammals, and how often the subject be provided with such a treatment and further one of the skill in the art would be required to research on long term and short term effects of providing the said exogenous gene sequences of DNA and cells in the patient. Accordingly, in view of the unpredictability in the art or guidance provided by the specification with regard to an enabled safe use of methods for treating any diseases or conditions and in sufficient numbers of claimed tissues/organs as of around the filing date of instant application and for the specific reasons cited above, it would have required undue experimentation for one of skill in the art to make and use the full scope of the claimed invention. At the

best the specification as filed is found only enabled for a method of cellular engrafting in a non-human mammal with cells transduced with a retrovirus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 3-5, 8-9 and 16-21 are rejected under 35 USC 102 (a) as being anticipated by Kiem et al., (1995, Curr. Opin. Oncol 7:107-14).

The above claims are directed to a viable cellular population transduced with retrovirus

Regarding claims 3-4 Kiem teaches a viable cellular populations of hematopoietic stem cells transduced with retrovirus or retroviral vectors and regarding claims 8-9 and 16-21 Kiem teaches a method of autologous transplantation of mammalian hematopoietic stem cells transduced with retroviral vectors into dogs (Abstract and pp.109, Table 1). The product 'retroviral transduced population of viable cells', irrespective whatever method was used for retrovirus transduction, is considered equivalent unless shown otherwise. Thus the rejected claims are within the scope of Kiem's disclosure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 3-5, 8-9 and 16-21 are rejected under 35 USC 103 (a) as being unpatentable over Moritz et al., (1994, The Journal of Clinical Investigation 93:1451-1457) and Nolta et al (1996, Proc. Natl. Acad. Sci. USA 93:2414-2419) in view of Papp et al., (1987 Biochim. Biophys. Acta 925:241-247).

The above claims are directed to a viable cellular population transduced with retrovirus and method for cellular grafting in mammal of the cells transduced with retrovirus. Given the scope of the instant claims, the claims are also rejected under 103.

Regarding claims 3-4 Moritz teaches a viable hematopoietic cell population infected with retroviruses (p.1452, col.2, 2nd paragraph). Further regarding above claims and claims 5, 8-9, and 16-21, Moritz teaches a method of transduction of cell with retrovirus in the presence of fibronectin fragments that were immobilized on Petri dishes (p.1452, col.1, 3rd paragraph). Moritz however, does not teach a method of engraftment of the cells transduced with retrovirus and does not teach the limitation of using a medium essentially free of hexadimethrine bromide.

Regarding claims 5-9, 18-21 Nolta teaches a engraftment of pluripotent hematopoietic cells (stem cells) that were transduced with retrovirus into a immune deficient (beige/nude/XID) mice (p.2414, Abstract).

Papp teaches a rationale regarding limitation in claims 3, 5, 8, 20 of using medium essentially free of hexadimethrine bromide (polybrene, a polycation) for transductions in presence of fibronectin. Papp teaches that complex formation of between heparin and fibronectin is inhibited in presence of polybrene (Abstract). Heparin binding domain of fibronectin is needed for ternary complex formation for the efficient transduction of retrovirus into mammalian cell in the instant invention.

Thus it would have been obvious for one of ordinary skill in the art to produce a retroviral transduced viable cell population by an enhanced transduction protocol involving the use of immobilized fibronectin as taught by Moritz and using a culture medium that is essentially free of polycations or polybrene (hexadimethrine bromide), as Papp teaches that it inhibits a interaction with heparin binding site of fibronectin. Further it would have been obvious for one of ordinary skill in the art to graft a viable

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pluripotent hematopoietic cells (stem cells) transduced with retrovirus under conditions as above into a non-human mammal for somatic gene transfer or clonal analysis. One of ordinary skill in the art would be motivated to use the method of retroviral transduction of cells in the presence of immobilized fibronectin and in a medium free of hexadimethrine bromide as it would enhance retrovirus transductions and facilitate a desired transgene introduction into cells that could be used for engraftment or somatic genetherapy. One of ordinary skill in the art would have reasonable expectation of success of generating a desired retroviral-transduced cell population using the efficient transduction protocol that involved the use of immbobilized fibronectin in a cell culture media that is essentially free of hexadimethrine and use the genetically engineered hematopoietic stem cells for engrafting or somatic genetherapy of a non-human mammal because of the teachings of Moritz, Nolta and Papp as above.

Thus, the claimed invention was *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 3 and 4 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2 and 19 of U.S. Patent No. 6,670,177 B2.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the present application and the claims 2 and 19 of the cited patent are drawn to a viable cellular population transduced by retroviral vector.

Accordingly, the claimed product in the present application and the cited patent are obvious variants. Therefore, the inventions as claimed are co-extensive.

Claims 3 and 4 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 20-22 of U.S. Patent No. 5,686,278.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the present application and the claims 20-22 of the cited patent are drawn to a viable cellular population transduced by retroviral vectors.

Accordingly, the claimed product in the present application and the cited patent are obvious variants. Therefore, the inventions as claimed are co-extensive

Conclusion:

No claim allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Kelaginamane Hiriyan* whose telephone number is (571) 272-3307. The examiner can normally be reached Monday through Friday from 9 AM-5PM. Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst *William N. Phillips* whose telephone number is 571 272-0548. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Dave Nguyen*, may be reached at (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see


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Kelaginamane T. Hiriyanne

Patent Examiner

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SUMESH KAUSHAL, PH.D.
PRIMARY EXAMINER

